IV. The Range of Perinatal HIV Prevention Interventions

Approaches Other than Short-Course AZT to Interrupt Mother-to-Infant Transmission, Including Low-Technology Approaches: Current Knowledge and Status of Ongoing Research

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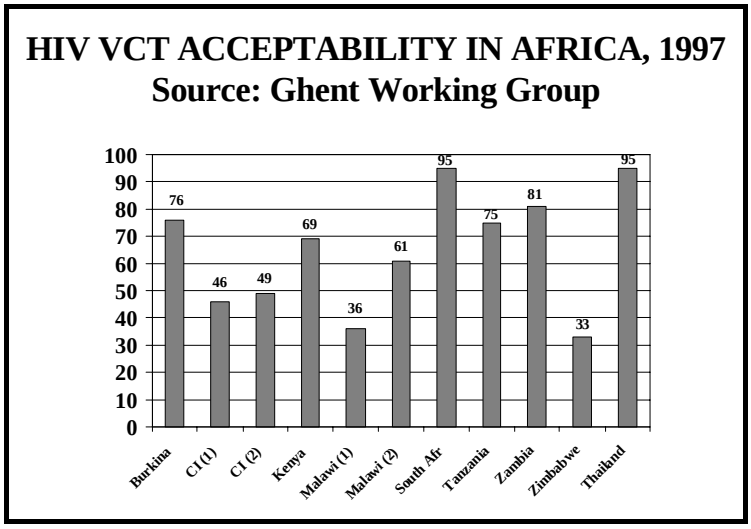
I will be presenting an overview of the approaches other than short-course AZT, including low-technology approaches, to reduce (and I do not think we can really interrupt) vertical transmission.

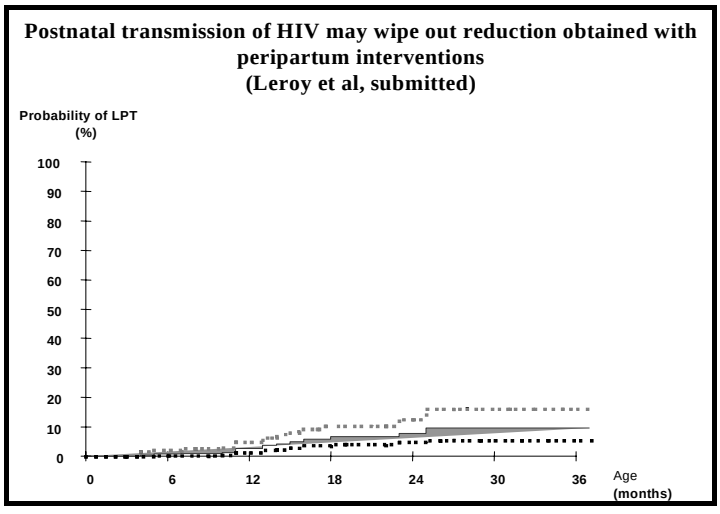
I will start with a few reasons why approaches other than short-course AZT are relevant and interesting. Then I will present an overview of ongoing research, including the research on antiretrovirals, of course, and then discuss each intervention by itself and where we are and when the results are expected to be available. I will finish by giving some perspectives on how we go from individual intervention to comprehensive programs.

My first proposal is that short-course AZT is only part of the solution that we have to look for, at least for the African continent. To remind you, in any given country in Africa where the HIV prevalence is high, the number of HIV-infected children that we expect is 10, 20, or even more times higher than in Thailand. So the magnitude of the problem we are dealing with is enormous. I believe we will be facing many problems with this.

The first problem is that, in Thailand, the reduction in transmission that has been obtained is 50 percent, and I do not believe that at the present time AZT in Africa with a similar or a comparable regimen could do any better. Thus, there is still room for improvement if we consider that at best we will reduce transmission by half. This indicates there is room for other approaches. The second problem is that counseling and testing is difficult to implement, which we heard in earlier presentations. The third one is that postnatal transmission is clearly an additional problem specific to the African population and to some others that we have to consider. And, finally, the cost of the intervention itself is not a totally resolved issue at the present time.



I will comment a bit more on counseling and postnatal transmission first. This slide describes a survey conducted last year in different centers, showing what is the current acceptability of antenatal testing by pregnant women. All these sites are in Africa, except the column on the extreme right which represents a site in Thailand. Previous presentations discussed that the range of acceptability, including both pre-test and post-test, varies extensively from approximately 33 percent to 95 percent, depending on the site. There also is room for improvement here, but it already tells us that we will not be able to accomplish, at least rapidly, good voluntary counseling and testing programs.



The second major problem that I just mentioned is the issue of postnatal transmission. What is reported on this slide is a compilation of data from observational cohorts; there is no intervention, so it shows the risk of what we call late postnatal transmission. In fact, you must consider that the y-axis, the vertical axis, starts at about 2 to 3 months of age, so it is skewed slightly more to the right. We looked as carefully as possible at the risk of postnatal transmission beginning at 2-3 months of age.

What you can see on this slide is that transmission through breast-feeding continues throughout the breast-feeding period at a rate of about 3 percent per year of breast-feeding. That clearly tells us that if we do not do anything about this problem, what we can obtain with peripartum interventions easily can be wiped out later on, presenting a major problem.

Regarding existing research, we have a number of different potential interventions that are being evaluated: antiretrovirals, vaginal disinfection, micronutrients, anti-HIV-specific immunoglobulins, and artificial feeding. There is only one trial of antiretrovirals completed in Thailand, as we know, and one trial of vaginal disinfection completed in Africa. All of the other trials, especially the ones in brackets, are ongoing. All of them, or at least most of them, stopped their placebo arm in February or March, but the results are not available at the present time, and we should not forget this. Thus, there are many trials, but many trials without results available at the present time.

OVERVIEW OF ONGOING RESEARCH (2)
ANTIRETROVIRALS

Sponsor	Country	Phase	Size (Arms)	Drug
ANRS	Burkina Faso, Côte d'Ivoire	II/III	416 (2)	AZT *
CDC	Côte d'Ivoire	III	275 (2),	AZT *
NIH / Harvard	Thailand	III	1500 ? (4)	AZT
NIH HIVNet	Uganda	II/III	1500 ? (3),	AZT *or nevirapine*
UNAIDS	South Africa, Uganda, Tanzania	III	1900 ? (4),	AZT and 3TC *

*vs placebo

Focusing now a bit more on the antiretroviral trials, I have indicated on this slide the five major ongoing antiretroviral trials. There are two others that are just beginning at the present time. However, these are the ones that are underway and almost ready to give us the answers.

The sample size I have put in the fourth column is the sample size which was reached before randomization was stopped and placebo arms were stopped in February. For most of the trials, at least the ANRS and CDC trials, the sample size obtained before randomization was stopped is below what was expected by the investigators. That means that in a few months these trials will provide results, but they may be slightly more difficult to interpret than we anticipated because of problems with sample size.

According to Joseph Saba, the UNAIDS trial finally enrolled almost the exact number that was anticipated. Only one trial uses a new compound called Neverapine, and this trial has just started.

To finish with the antiretrovirals and go to low-tech technologies or other technologies, I would just like to pose three main questions. I realize that some of you are frustrated with having more questions than answers, but still I see at least three major questions and potentially a fourth one to raise regarding antiretrovirals, with no answer to give you.

The first question is: Does short-course AZT reduce vertical transmission around 3 or 6 months of age when breast-feeding has been the predominant or almost exclusive method of infant feeding in these trials? This is clearly an essential question. Can we reproduce in Africa the results obtained in Thailand? I believe in 3 to 6 months this answer will be available, and I suspect we will have some good results, but it is still unclear.

The second question, which is perhaps not as important, is: Does a short-course AZT regimen reduce vertical transmission at the end of breast-feeding? At least in the ongoing trials, breast-feeding has continued to a certain extent for several months or up to a year or even more. It will be extraordinarily interesting to see what happens in terms of overall transmission rate when the investigators have not been able to get clear reduction of the risk of postnatal transmission with the population they were dealing with.

The third question is: Does a short-course combination of antiretrovirals perform better than AZT alone? This combination therapy is what the UNAIDS trial is evaluating. They are not evaluating the combination of therapy versus AZT alone, but when we get their results, we will see indirectly if two drugs do better than one drug. Perhaps this information will be quite essential for policy and strategy decisions.

The last question regarding antiretrovirals is: Can we do as well with a simpler regimen of antiretrovirals? I am referring here to drugs such as Nevirapine that can be given once within a few days of delivery, which would be even simpler than the current regimen of AZT.

The first three questions probably will be answered within 6 months. However, for the last question about Nevirapine, I believe we will wait much longer for that information.

Moving to lower tech approaches, let me briefly discuss vaginal disinfection. We have known for at least 6 years that administering Chlorhexidine during labor reduces the risk of child morbidity caused by streptococcus infection. This was well demonstrated in a randomized trial in Sweden. There was no HIV infection involved in this trial, but the

concept provides the basis, or rationale, for evaluating such an intervention with HIV. Chlorhexidine and other compounds such as benzalkonium chloride are well known to obstetricians to be antiseptic and virucidal agents against HIV. This was demonstrated in vitro. It was not as clear in vivo, but was still worth trying. The objective a few years ago was to see whether peripartum transmission could be reduced with a cheap, acceptable, and well-tolerated intervention such as this one.

I will not report on the trial we performed in Burkina Faso and Côte d'Ivoire, which was a phase II tolerance and acceptability trial of benzalkonium chloride started at 38 weeks of gestation. The results of this trial will be reported in Geneva next month. I can say that the tolerance and acceptability is extremely good, even better than with antiretrovirals, but that our sample size did not allow us to look at efficacy and we have not planned an efficacy trial on this.

On the other hand, a phase III trial that was conducted in Malawi, on which results were published 2 years ago, compared Chlorhexidine with using no intervention. As you may remember, the overall result was absolutely negative in the sense that there was the same risk of transmission in the Chlorhexidine arm and in the no-intervention arm.

Nevertheless, in the subgroup of patients who had premature rupture of membranes of more than 4 hours, which is a well-know risk factor of transmission, there was a spectacular effect in reducing transmission which was promising and told us that much is going on in the peripartum period that is worthwhile to address, even if overall we do not have a significant result.

In the same trial, the researchers looked at early neonatal mortality or maternal hospital admissions as a proxy for maternal infections. In the Chlorhexidine group, there was a substantial reduction in the risk for these two outcomes–about 50 percent for neonatal mortality and a little bit less for maternal hospital admissions. That tells us that this type of approach, even if it does not reduce directly the risk of transmission, can be very relevant to the improvement of health in the context of high HIV prevalence. There are not many interventions for which we have a randomized trial available in Africa, and we should consider these results as extremely informative.

To continue with the discussion of vaginal disinfection, there is another trial in Kenya, in Mombasa, that is ongoing and unpublished, but Dr. Marlin Timmerman kindly gave me some information that I could report to you. Again, this information is not extremely promising. For the estimated risk of transmission at 6 weeks postpartum, absolutely no difference with regard to vertical transmission was noted. But this is still ongoing and other outcomes have not been examined at this time.

Moving now to vitamin A supplementation, we know that vitamin A deficits are common in some parts of Africa, but not everywhere. It is unclear whether there is much deficit in the urban populations in West Africa, for instance. In some parts of Africa, however, deficits are well known.

Since 1994, observational studies in Malawi and in Kenya have concluded that when

there is a maternal deficit in vitamin A, the risk of transmission is increased. Maybe the causal relationship between this deficit and transmission is not entirely clear, but this is an interesting piece of evidence.

There was some concern in dealing with supplementation, but in the past 2 years two of these concerns have been, I believe, minimized. One concern was that, in supplementing vitamin A, HIV replication could increase; the other concern was that the risk of teratogenicity was possible. I do not think we have any new information in this area, and we can consider these two deleterious effects as possibly rare or nonexistent with supplementation.

Therefore, if supplementation is safe, it is certainly cheap, acceptable, and would not require counseling again, making it quite interesting for our purpose.

Where do we stand at the present time? There is a large trial in Malawi for which results have been postponed for a bit. The investigators had problems with the measurement of the judgment criteria. But I believe in a few months these results should be available.

In South Africa, in Durban, results may come very soon. In fact, they have their Data and Safety Monitoring Board meeting next week, and perhaps results may come out of this.

Interestingly, I have a big question mark on the Tanzania trial conducted by a team from Harvard; we have just learned that some of these results may be available in a few days, and that some positive results are expected on infant growth and infant health, but no results are available at this time on the reduction in transmission rate.

In Zimbabwe, a trial is examining a more general approach of supplementing with 13 micronutrients, and the results are pending. We do not know when data will be available. Another trial in Zimbabwe is considering a very interesting approach of supplementing mothers and infants to reduce the risk of postpartum transmission only. This is a very promising approach, but they started enrollment only a few months ago. It is much too early to say what will happen with that study.

To finish with vitamin A, a complimentary approach that is also low tech but slightly beyond the scope of our workshop, is to consider that vitamin A supplementation could be beneficial to HIV-infected children themselves. There was a small-scale trial in Durban a few years ago that found a slight beneficial effect. There currently are two trials on this topic, one in Uganda and the other in Zimbabwe (the trial I was referring to previously regarding postnatal transmission). The Zimbabwe trial looks also at the improvement of child health.

To finish this overview of the different interventions, I will remind you that there is one trial ongoing in Nairobi comparing bottle-fed and breast-fed babies. We have been waiting for the results of this trial for more than a year now. But I checked last week, and there still is no result available. That is an important piece of information we lack.

Nevertheless, with antiretrovirals and breast-feeding, I believe UNAIDS, WHO, and UNICEF have already taken the lead in making some policy decisions, and I think we should congratulate them despite the fact that, as you saw, all the answers are not available at the

present time. In this slide, I have added a statement from a press release issued last month by UNAIDS, which said that, "There is a need to support alternatives for breast-feeding for mothers who test positive for HIV with methods appropriate to their situations." That, to me, is a very new and essential step forward.

In conclusion, individual interventions have been evaluated, but we are far from having comprehensive programs. What we are looking at is potentially more a combination of interventions than individual interventions. As a basis for that, we should see it is not even reasonable to consider any of these interventions if the basics of the continuum of care that we need are not guaranteed. We know that in many African settings it is not. Thus, if we cannot guarantee a high quality of basic antenatal, obstetrical, and child care services, I believe it is not reasonable to consider either the low-tech solutions I have discussed or falsely promote high-tech technologies such as antiretrovirals.

To conclude, I would propose two situations. In the first situation, voluntary counseling and testing is not part of routine care. What can we really propose for HIV-infected pregnant women? I believe that we can consider only vaginal disinfection and vitamin A supplementation in the few weeks we will have. Certainly we should not forget in this context to look at reduction in vertical transmission, but perhaps reduction in maternal and infant morbidity and mortality, in general, is the best we can expect.

In the second situation, if counseling and testing services are or are planned to be part of routine care, access to alternatives to breast-feeding is the very major issue to address with short-course AZT or combination of antiretrovirals, depending on the results that are obtained in a few weeks or months.

In my opinion, the approach of vaginal disinfection is interesting, but I do not know about vitamin A supplementation.

Although we have focused primarily on peripartum interventions or postpartum interventions, we should not forget the other ways we can work on reducing HIV vertical transmission. In reducing HIV transmission to women and providing access to family planning for HIV-infected women, we also have clear-cut ways to reduce the risk of vertical transmission.

Perinatal Prevention Program Options, Simple to Complex

Presented by Isabelle DeVincenzi, M.D.
UNAIDS

I would like to change the title of my presentation by taking off "simple to complex" since, if it is true that there are several program options according to the context, none of these options is simple.

The most simple program would probably be to offer pills of antiretrovirals for

1 month to pregnant women known to be HIV-positive, but we know that in developing countries less than 5 percent of HIV-infected individuals know their serostatus. Therefore, offering antiretrovirals to the few women who know their status would probably make little difference in the number of infected children.

Furthermore, we still do not know what the efficacy of antiretrovirals is for breast-fed children, but this efficacy may be significantly lower than for non-breast-fed children. For UNAIDS today, it makes little sense to offer antiretrovirals without increasing access to an adequate alternative to breast-feeding.

The simplified model shown on this slide indicates the key steps to reduce transmission from infected mothers to children. The aim of this model is to map the process of implementing interventions which are known to reduce mother-to-child transmission of HIV, that is, antiretrovirals and avoidance of breast-feeding. It may also help to identify, in a given situation, which interventions are critical or most cost-effective to reduce the number of cases of mother-to-child transmission of HIV.

The model starts from a population of pregnant women in a given responsibility area (e.g., city, district, region, or country) with a given HIV prevalence. First, a woman has to reach antenatal care services in a timely manner to benefit from interventions which will be offered. This requires that basic antenatal services be in place. For example, screening for and treating anemia, which already are recommended for all women, may be an important component for monitoring antiretroviral treatment. The first arrow in the model thus represents the proportion of pregnant women who reach the antenatal care service early enough to receive adequate antenatal care, be counseled and tested, and begin antiretroviral treatment at 36 weeks of pregnancy.

The second step concerns confidential and voluntary HIV counseling and testing services, which should be widely available and accepted in order to identify women who might benefit from specific interventions. The second arrow represents the proportion of women being counseled and tested among those reaching antenatal care services.

Women have to get their results after testing, and ideally antiretrovirals should be available and affordable for all known HIV-infected women. Ideally again, known HIV-infected women should feed their infants with adequate breast milk substitutes, and conditions for safe alternative feedings should be in place.

The last arrow represents the efficacy of interventions prescribed and adequately taken.

If we apply the model to the situation in Harare, for example, we can identify what are the critical steps and therefore where program planners should put their efforts. In Harare, the HIV prevalence is about 30 percent among pregnant women. Seventy percent of pregnant women get antenatal care. A very small proportion of women (less than 5 percent) are offered testing and counseling. In an ongoing trial looking at the benefit of vitamin A supplementation, the return rate for test results was only 33 percent. ZDV is available for a small minority, a minority of whom also can afford breast milk substitutes. In

such a situation, the expected number of infections averted by antiretrovirals and avoidance of breast-feeding by a small minority of women is less than 1 per 10,000 infants born. Offering ZDV and an alternative to breast-feeding to all women known to be HIV-positive will make no difference since these women are few. In such a situation, an essential step will be to implement interventions to increase access, uptake, and return rate for testing and counseling services while at the same time widening access to antiretroviral treatments.

Some of the factors affecting the proportion of women knowing their HIV status are the availability and accessibility of voluntary counseling and testing services; the public awareness of the risk of HIV infection; the acceptability of the services (which will depend on quality of counseling, confidentiality, social tolerance, ability to cope with results, availability of treatment and support services, etc.); and the time of booking for antenatal care, which is an important factor since it often takes 2 weeks to get the test result (if rapid testing is not used). An example of an activity that may increase the proportion of women knowing their HIV status is increased access to counseling and testing for the general population; for example, it has been reported that some women were not able to cope with their test results during pregnancy, but returned to get their results after delivery. It thus may be important to increase access to testing and services outside the context of pregnancy. But, even if pregnancy is not the best moment to learn of positive results, integration of voluntary counseling and testing services in antenatal care will be important. Other potential activities are the development of specific communication programs to promote testing and counseling, such as programs of social marketing; the development of support services for HIV-positive individuals to increase their acceptability of the test; training of staff on HIV issues and increasing staff motivation through specific communication strategies; and eventually using rapid and simple test kits which may help to increase the number of women tested who will get their test results.

Even if health authorities cannot provide antiretrovirals and infant formula to HIV-infected mothers identified, they should at least provide infant-feeding counseling. Adequately used commercial infant formula is the best option, but there are other options that may be more affordable, such as home-prepared formula, which is modified animal milk; early cessation of breast-feeding; expressing and heat-treating breast milk; using a milk bank; and wet nursing. These options are detailed in the UNICEF-WHO-UNAIDS guidelines on HIV and infant feeding.

Besides individual infant-feeding counseling, other activities may increase the proportion of women using safe breast-feeding alternatives: making safe alternatives available and affordable for families, and conducting research on replacement feeding other than infant formula and more importantly the safety of different options assessed (indeed, no research at all has been done on other infant feeding options than breast-feeding for the past 20 years). An hygienic environment should be promoted, as well as an environment empowering women to carry out their decision.

If voluntary counseling and testing is to be promoted, it will be necessary to inform

HIV-positive women about the benefits of antiretrovirals and how to get treatment. Affordability may be increased by decreasing the cost of the drug through national and international negotiations with pharmaceutical companies. Availability could be increased by organizing sustainable distribution systems whether the women will have to pay for the drug or not. Health care workers in the public and private sectors will have to be trained in prescription and monitoring of antiretroviral treatments.

Unfortunately, it will not be possible to make HIV testing and counseling and adequate alternatives to breast-feeding accessible soon to all women in all developing countries. However, where the health services and/or cultural norms do not allow implementation of these interventions, other interventions can reduce mother-to-child transmission and also prepare the field for the introduction of antiretrovirals.

- As has already been said and repeated, the first goal is to apply standards of care for all women. That is to say, make antenatal care accessible to all women, ensure that basic services are given such as screening and treatment of anemia or syphilis, and ensure adequate obstetrical procedures avoiding unnecessary invasive procedures and blood transfusion.
- Developing communication strategies regarding benefits of adequate care will be important since it may increase willingness of women to use these services.
- Providing micronutrient supplementation where needed will have a global benefit for mother and child health and may also reduce mother-to-child transmission.
- In addition to the global health benefit and the potential reduction of mother-to-child transmission, widened screening for and treatment of STDs antenatally may have an important impact on the primary prevention of HIV infection among pregnant and lactating women.
- Implementing HIV/STD counseling and access to condoms will, again, prevent HIV infection in women and therefore in their future children.
- Strengthening family planning will reduce the number of unwanted pregnancies.
- Vaginal lavage may also be considered to reduce postpartum infections and may also reduce mother-to-child HIV transmission.

We tend to focus on the infant's health, with some consideration for the mother's health, but I would like to re-emphasize that mother-to-child transmission interventions must be part of a comprehensive approach, both to HIV prevention and care and to antenatal care. Such an approach takes into account the following:

- Primary prevention of HIV infection is the best way to reduce the burden of the HIV epidemic in children.
- Most HIV-infected women in developing countries have been infected through heterosexual sex with their regular partner and, therefore, women should not be stigmatized as vectors of transmission to infants.
- To make testing acceptable, support services should be accessible for HIV-positive women and children after discharge from mother-and-child health services.

- The health and well-being of mothers and other children should not be altered by the intervention. For example, breast-feeding should still be promoted in the general population.
- Resources should not be taken from those available or needed for basic antenatal care and related programs.

Mother-to-child transmission interventions undertaken separately from these other measures probably are of limited benefit to public health and may pose ethical problems. In conclusion, strategic planning should be based on a situation assessment which will help to identify which interventions are needed, taking into account effectiveness, costs, and expected social acceptability. The minimum package of the intervention should include strengthening of antenatal care, family planning, and STD/HIV counseling. This is a package which will be promoted in rural areas of Burkino Faso, for example, where the coverage of antenatal care still is very low.

An intermediate option will be to add to the minimum package easy access to prenatal voluntary HIV testing and counseling with the possibility of referring HIV-positive women for further care and support. Such counseling should include information on infant feeding options and family planning. This kind of package is planned to be introduced in Kenya soon.

The complete package would include increasing access to affordable antiretrovirals and alternatives to breast-feeding. This is what is being done in Brazil and Thailand already, and is planned to be introduced in several other countries in Asia and Africa. In Zimbabwe, for example, a proposal for the starting phase in the two main cities of the country is already developed.